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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

MAR 1 1996

Food and Drug Administration
Rockville MD 20857

Peter S. Reichertz, Esquire
Arent, Fox, Kintner, Plotkin & Kahn
1050 Connecticut Avenue, NW
Washington, DC 20036-5339

Re: Docket No. 78N-036L
Comments No. CP14, SUP8,
AMD10, LET71, and SUP11

Dear Mr. Reichertz:

This letter concerns your citizen petition submitted on behalf of C. B. Fleet Company, Inc., dated March 23, 1993, and additional data and information submitted on December 22, 1993, June 13, 1994, and January 18, 1995. The submissions are identified as CP14, SUP8, AMD10, LET71, and SUP11, respectively, filed under Docket No. 78N-036L in the Dockets Management Branch. You requested that the tentative final monograph for OTC laxative drug products (published in the FEDERAL REGISTER of January 15, 1985, 50 FR 2124) be amended to include two 45 milliliter (mL) doses of dibasic sodium phosphate/monobasic sodium phosphate solution (sodium phosphates oral solution, U.S.P.) in sequential administration 10 to 12 hours apart as a bowel cleansing system.

Your March 23, 1993 citizen petition contained a published clinical study by Vanner et al. (Ref. 1), an unpublished report by Del Piano et al. (Ref. 2), six abstracts (Refs. 3 through 8), and a section of a textbook (Ref. 9). Your December 22, 1993 letter contained the following: (a) your response to comments submitted by Braintree Laboratories; (b) a study by Kolts et al. (Ref. 10), which was previously provided as an abstract (Ref. 3), (c) your comments that "Fleet has not yet received any reports of serious side effects from the use of the regimen described in the citizen petition;" and (d) brief information on a recently completed clinical study (Ref. 11) of two sequential doses of sodium phosphates oral solution as a colonic preparation in 450 subjects. The study had not yet been completed and the institution where the study was done had requested that it not be distributed at that time. Your June 13, 1994 letter contained

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the unpublished report of the study (Ref. 11) mentioned in your December 22, 1993 letter, five abstracts (Refs. 12 through 16), and material presented at a postgraduate course given in May 1994 (Ref. 17). Your January 18, 1995 letter contained a new study by Huynh et al. (Ref. 18).

We have reviewed your submissions and other data pertaining to sodium phosphates and determined that the data are insufficient to demonstrate the safety of two 45-mL doses of sodium phosphates oral solution in sequential administration 10 to 12 hours apart. Therefore, based on the existing information, two 45-mL doses of sodium phosphates oral solution in sequential administration 10 to 12 hours apart as a bowel cleansing system will not be included in the final monograph for OTC laxative drug products at this time.

We have the following specific comments regarding the data submitted in support of your petition: You did not categorize the submitted studies into pivotal and supportive clinical studies. Your submissions included three published, controlled clinical studies (Refs. 1, 10, and 18) on sodium phosphates oral solution administered as a bowel cleansing system. Thus, we reviewed these three studies as the pivotal studies to determine the safety and effectiveness of two 45-mL doses of sodium phosphates oral solution in sequential administration 10 to 12 hours apart as a bowel cleansing system.

In the first study, Vanner et al. (Ref. 1) compared a standard polyethylene glycol (PEG) based gastrointestinal solution to a sodium phosphates oral solution prior to colonoscopy. In this parallel, single-blinded, randomized study, 54 subjects received two 45-mL doses of the sodium phosphates oral solution 11 hours apart, and 48 subjects received 4 liters (L) of the PEG solution. The subjects had blood tests on admission and the morning of the procedure. The authors concluded that the sodium phosphates oral solution was safe and effective because serial measurements of blood tests, postural pulse, and blood pressure changes did not reveal any clinically significant changes in intravascular volume. One "syncopal episode" occurred in the sodium phosphates group. The authors mentioned that the subject's vital signs did not appear to indicate that hypovolemia was the cause. The authors reported that hyperphosphatemia occurred with sodium phosphates, but serum phosphate values returned to normal within

24 hours, and no concomitant decrease in calcium was seen. They added that histological assessment of the rectal mucosa for possible preparation-induced changes revealed no difference between the two drugs.

We note that numerous induced electrolyte abnormalities occurred in this study. The data showed statistically significant decreases in potassium and increases in hematocrit, sodium, chloride, osmolarity, and phosphate. Extreme serum phosphate levels reached 11.6 milligrams (mg)/deciliter (dL) in the sodium phosphates group and 4.7 mg/dL in the PEG group; normal values are 2.5 to 4.1 mg/dL. In hyperphosphatemia, excessive complexing of calcium with phosphate may contribute to a decrease in plasma ionized calcium, which results in hypocalcemia. Calcium levels were not reported for the entire sodium phosphates group nor was the risk of hypokalemia mentioned. The postural changes in pulse, systolic blood pressure, and the one "syncopal episode" were reasonably related to decreased intravascular volume in subjects in the sodium phosphates group.

Because elevated phosphate levels are known to occur with sodium phosphates use, 15 subjects were randomly selected to have serum phosphate and calcium levels measured at 4:00 p.m. on the day of colonoscopy and at 8:00 a.m. the following day. Seven of the 15 subjects received the sodium phosphates regimen. Vanner et al. reported that 2 hours after the second dose, the mean serum phosphorus was 7.2 mg/dL (nearly twice the prestudy value of 3.7 mg/dL), while the total calcium values continued to decline for at least 24 hours after the dose was taken.

We believe that the Vanner et al. study showed that postural increases in pulse, decreases in systolic blood pressure, and serum electrolyte and plasma volume shifts were greater in the sodium phosphates group than in the PEG group. The incidence of postural elevation in heart rate, indicating significant reduction in intravascular volume, was also three times higher in the sodium phosphates group than in the PEG group. Because of the small sample size, the fact that none of the study subjects died or had serious side effects that required hospitalization cannot be interpreted to mean that two 45-mL doses of sodium phosphates oral solution are safe to take without a physician's supervision.

In the second study, Kolts et al. (Ref. 10) conducted a single-center, single-blind, parallel, controlled clinical study to evaluate the safety and efficacy of sodium phosphates oral solution as a bowel cleansing system for colonic preparation. The investigators sought to replicate the results published by Vanner et al. (Ref. 1) on the safety and efficacy of sodium phosphates. The investigators also attempted to evaluate the safety and efficacy of a 95 percent castor oil product as a colonic preparation for colonoscopy.

One hundred and thirteen subjects were randomized to a standard PEG solution, sodium phosphates oral solution, or the castor oil product. At 6:00 p.m. the evening prior to the colonoscopy, 38 subjects received 4 L of the PEG solution (240 mL every 10 minutes), 34 subjects received 45 mL of sodium phosphates oral solution in 45 mL of water, and 41 subjects received 60 mL of castor oil. Subjects receiving the sodium phosphates or castor oil were instructed to drink at least 90 to 360 mL of water 1 hour after receiving the solutions. All subjects received nothing by mouth after midnight. Subjects in the sodium phosphates group received 45 mL of the solution in 45 mL of water at 6:00 a.m. on the day of the procedure.

The investigators reported that both sodium phosphates and PEG were significantly better for bowel cleansing than castor oil, and that both sodium phosphates and castor oil were significantly easier to completely ingest than PEG. The investigators reported that sodium phosphates oral solution was better in achieving an excellent (38 percent) or good (41 percent) cleansing score, compared with PEG (32 percent and 29 percent) or with castor oil (20 percent and 12 percent).

Although no clinical manifestations of hypocalcemia were reported, the independent evaluation of serum phosphate and calcium concentration in 5 subjects who took sodium phosphates showed a significantly greater mean serum phosphate concentration over mean baseline value 2 hours after the second sodium phosphates dose. There was a significant mean serum phosphate concentration increase of 3.5 ± 1.6 mg/dL, important because hyperphosphatemia can cause hypocalcemia and increased neuromuscular excitability. Reportedly, the mean serum calcium concentration also decreased in the 5 subjects evaluated

(individual subject data were not presented in the publication). The mean phosphate and calcium concentrations normalized after 10 hours, and the mean serum phosphate concentration returned to baseline after 24 hours. Neither muscular spasms nor clinically overt tetany was reported.

In the third study, Huynh et al. (Ref. 18) assessed the safety profile of sodium phosphates oral solution to determine whether clinically significant hypocalcemia and hypovolemia would be near the threshold for causing serious side effects. Fifty subjects (27 outpatients and 23 inpatients) were each given a 45-mL dose of sodium phosphates oral solution at 10 hours and again at 15 hours (two doses 5 hours apart) before colonoscopy. Subjects with renal failure, active heart disease, ileus, and gross ascites were excluded. All subjects were on a liquid diet for 24 hours prior to the colonoscopy and were encouraged to drink fluids liberally during the colonic lavage phase. The investigators stated that intravenous fluid replacement was used for some inpatients in this study, but the number of inpatients on intravenous fluid replacement was not specified. The investigators reported that sodium phosphates oral solution is safe for colonic cleansing in most subjects, even when using a 5-hour regimen. However, they also stated that because some subjects developed asymptomatic intravascular volume contraction and borderline hypocalcemia, sodium phosphates oral solution may have a lower therapeutic index than other bowel cleansing drugs.

You indicated that C. B. Fleet believes that this study provides the necessary evidence to demonstrate that two 45-mL doses of sodium phosphates oral solution are safe for use 12 hours apart. We believe that the study did not provide sufficient evidence to support your petition. The publication lacked data for individual subjects such as baseline medical conditions, concomitant diseases and medications, laboratory and vital sign data, fluid intake, ages and genders, and adverse drug reaction profiles.

We also believe that this study did not provide sufficient evidence that two 45-mL doses of sodium phosphates oral solution given 5 hours apart are safe. The investigators reported that intravascular volume depletion was clinically significant in 40 percent of the inpatients and 7 percent of the outpatients, respectively. The investigators indicated that the hypocalcemia

observed in some of the subjects was minor and probably reflected increased sensitivity of ionized calcium measurements used in this study because no subject complained of paresthesia or numbness. The investigators stated that some experts in calcium metabolism suggest that minor perturbations in ionized calcium levels below the established normal range, such as described in this study, should not cause symptoms that would be harmful to the patient. However, we note that the article states that such patients may develop asymptomatic intravascular volume contraction and borderline hypocalcemia. The authors also mentioned that sodium phosphates has a lower therapeutic index than other agents and that, in some circumstances, alternate colonic cleansing agents should be used. In addition, hypokalemia can occur with sodium phosphates use, but the investigators failed to monitor potassium levels in this study. Further, most inpatients were on intravenous fluid replacement, which is not routinely administered as part of a colonoscopy procedure. Finally, subjects in the study should have been primarily outpatients if the product is to be promoted for outpatient use. Thus, we do not find this study adequate to support your petition or the safety of a 5-hour bowel cleansing regimen.

We believe that the three studies (Refs. 1, 10, and 18) provide evidence of the effectiveness of two sequential doses of sodium phosphates for bowel cleansing for colonoscopy in adult subjects. However, the studies did not demonstrate the safety of two 45-mL doses of sodium phosphates oral solution in sequential administration 10 to 12 hours apart as a bowel cleansing system. Along with vital signs and clinical evaluations, monitoring of ionized calcium, phosphorus, potassium, and sodium levels in all subjects should be obtained at baseline, at specific intervals throughout the study, and until all values have returned to baseline after the second sodium phosphates dose is given in order to provide a complete safety profile of this dosage regimen.

The following two unpublished studies were submitted in support of your petition. The first study by Del Piano et al. (Ref. 2) compared three different methods in colonoscopy preparation in a randomized study in 150 subjects (ages 33 to 84 years of age, average age 58 years), using 50 subjects per group. The first group was randomized to a 3-day preparation of a liquid diet, a

cathartic, and an enema; the second group was randomized to 4 L of PEG solution; and the third group was randomized to four doses (20 mL each) of a sodium phosphates oral solution containing 48 grams (g) of monobasic sodium phosphate and 18 g of dibasic sodium phosphate per dL. The total 80 mL dose of the sodium phosphates oral solution used by Del Piano et al. is equivalent to 38.4 g of monobasic sodium phosphate and 14.4 g of dibasic sodium phosphate. This total 80 mL dose is about 12 percent less than the total sodium phosphates 90 mL dose tested by Vanner et al. and Kolts et al.

The day before the exam, subjects in one group ingested PEG solution (time not given). The subjects in another group were given a two dose regimen (40 mL each) of sodium phosphates at 4:00 p.m. and 8:00 p.m., 4 hours apart. Both doses were followed by 1 to 2 L of oral fluids. Serum electrolytes, including sodium, potassium, calcium, and phosphorus, were obtained before and after the endoscopy. The investigators reported that the sodium phosphates and the 3-day preparation were significantly more effective ($p < 0.01$) than PEG in reducing the volume of fluid flowing out during the endoscopy. However, the sodium phosphates group experienced increased mean serum phosphorus and decreased mean serum calcium concentrations. No muscular spasms, tetany, or adverse clinical reactions were reported. This study does not support the times of administration and doses of sodium phosphates requested by your petition. In addition, the investigators did not demonstrate the safety of the sequential doses of sodium phosphates compared to alternative therapies.

In a randomized, endoscopist-blinded, unpublished study by Cohen et al. (Ref. 11), 422 subjects received either standard PEG colonic lavage (138 subjects), a newer sulfate-free 4 L PEG solution (PEG-SF) (141 subjects), or a sequential two-dose regimen of 45-mL sodium phosphates oral solution as a bowel cleansing preparation (143 subjects). The sodium phosphates was administered at 4:00 p.m. and 6:00 a.m. (14 hours apart). Before and after study participation, all subjects were weighed and serum electrolytes as well as phosphate, magnesium, calcium, and osmolarity were measured.

Although statistically significant differences were noted in all parameters measured (except blood urea nitrogen), the investigators stated that none of the changes was clinically

significant. However, in our view, this study does not adequately demonstrate the safety of two 45-mL doses of sodium phosphates oral solution in sequential administration 10 to 12 hours apart as a bowel cleansing system. The subjects in the sodium phosphates group lost more weight and experienced more electrolyte and osmolarity changes than those in the PEG groups. Ionized calcium levels and normal serum electrolyte ranges used to determine the biochemical changes were not given. Values presented in tables of the study were inconsistently reported, sometimes as means and sometimes as medians. Statistical "p" values for certain comparisons were presented differently in the text versus the tables. In addition, the time interval between doses in this study was longer than the time specified in the petition.

The Cohen et al. study may provide electrolyte and clinical data on the safety of the two doses of 45-mL of sodium phosphates oral solution given 14 hours apart. However, individual subject data are needed to completely evaluate: (a) any relationship to demographics (age), prior medical history or concomitant illness, electrolyte shifts, and adverse event reports; (b) any relationship of timing between doses taken and adverse events; (c) recovery timeline from any experienced adverse event; and (d) any relationship between effectiveness and compliance with the regimen. In addition, normal ranges for the laboratory values listed in table 3 of the study need to be provided with some explanation of serum calcium levels in relationship to albumin and other factors that may affect ionized calcium (or measured ionized calcium levels).

You also submitted eleven abstracts (Refs. 3 through 8, and 11 through 16) in support of your petition. However, these abstracts did not adequately document the safety of the sequential dose bowel cleansing system mentioned in the petition.

Lyles et al. (Ref. 3) was an abstract of the Kolts et al. study (see the above discussion for reference 10).

Haroon and Iber (Ref. 4) conducted a randomized clinical trial to determine the oral tolerance, safety, and effectiveness of sodium phosphates oral solution for bowel cleansing prior to colonoscopy. Thirty-six adult subjects (18 subjects per group) between 65 to 92 years of age (mean age was 73 years) were

randomly assigned to be treated with sodium phosphates oral solution or PEG. One group took two 45-mL doses of sodium phosphates oral solution diluted with 90 mL of water 11 hours apart. The other group took 4 L of PEG on the evening of admission. The efficacy endpoints, safety monitoring, and formulations used were similar to those described in the Vanner et al. and Kolts et al. studies. The report indicated that the "degree of colonoscopic cleansing" was significantly greater in the sodium phosphates group in comparison to the PEG group (excellent = 71 percent versus 53 percent, respectively). The sodium phosphates regimen was reported to be easier to complete, and was associated with less nausea, vomiting, abdominal discomfort, and diarrhea.

Sodium phosphates was reported to produce more depletion of water and electrolytes with a decrease in potassium and a significant increase in serum phosphorus, sodium, chloride, and osmolarity. Calcium concentration was not provided. The report states that approximately 90 percent of the electrolyte changes remained within the normal laboratory ranges, and values returned to baseline within 24 to 48 hours. Therefore, the investigators concluded that sodium phosphates is a safe and well-tolerated oral colonic preparation for older individuals, and that it produces better colonic cleansing than PEG.

Reanalyzed by chi-square and Fisher's Exact Test, there is no significant difference in bowel cleansing between the two treatment groups. However, the information provided in the abstract indicated that at least two subjects in the sodium phosphates group had a significant abnormal increase in serum phosphorus, sodium, chloride, and osmolarity. This safety information is critical because renal clearance is diminished in older subjects and the elderly may be at risk for hyperphosphatemia, hypocalcemia, convulsions, and tetany with sodium phosphates use.

Clarkston et al. (Ref. 14) compared PEG to a sodium phosphates oral regimen for bowel cleansing prior to colonoscopy. In this randomized trial, 26 subjects took 4 L of the PEG solution and 25 subjects took two 45-mL doses of sodium phosphates oral solution 11 hours apart. The subjects had a chemistry panel and ionized calcium done prior to taking the drug and on the morning of the colonoscopy. The results indicated that the sodium phosphates

oral solution caused a decrease in ionized serum calcium and serum potassium, with concomitant increases in phosphate. The investigators stated that the sodium phosphates oral regimen resulted in statistically significant changes in serum sodium, potassium, phosphorus, and calcium ($p < 0.01$). The investigators concluded that the risk of symptoms of hypocalcemia must be considered due to the abnormal low levels of ionized calcium that frequently occur with this regimen.

Our review of this abstract shows that the majority of the subjects experienced hyperphosphatemia with this sodium phosphates regimen. The large reductions in ionized serum calcium and serum potassium were of particular concern. Therefore, we do not believe this abstract can be used to document the safety of two 45-mL doses of sodium phosphates oral solution given 11 hours apart, as a bowel cleansing regimen.

Stone et al. (Ref. 15) randomized 45 subjects to either 4 L of PEG solution (25 subjects) or two 45 mL dosages of sodium phosphates oral solution (30 subjects) before elective outpatient colonoscopy. The authors reported that hypoxia and cardiac arrhythmias were not significantly different in the two groups. This abstract is inadequate because the time sequence for the PEG and sodium phosphates was not given. However, we note that hypotension occurred more often with sodium phosphates (14/30 subjects) than PEG (5/25 subjects), and that more subjects receiving sodium phosphates required intravenous fluid boluses to maintain hemodynamic stability during colonoscopy.

Thomson et al. (Ref. 16) randomized 116 subjects to receive PEG (55 subjects) or sodium phosphates (61 subjects) before colonoscopy. The subjects reported that sodium phosphates was slightly more tolerable than PEG, although the difference was not statistically significant. The colonoscopists found no difference in the quality of the bowel preparation. However, we note that the sodium phosphates subjects developed hyperphosphatemia (value not given) and a lower mean serum potassium of 3.8 millimoles (mmol)/L than the PEG group (4.2 mmol/L).

Individual subject data for analysis from the two abstracts (Refs. 15 and 16) may allow a better evaluation of safety issues related to the requested sequential dosing regimen. We suggest

that the company obtain data from the individual investigators.

We have reviewed the other abstracts and do not consider them sufficient for the following reasons. Several authors did not provide the time sequence and amount of sodium phosphates oral solution given: Golub et al. (Ref. 5), Raymond et al. (Ref. 7), and Rossetti et al. (Ref. 8). Afridi et al. (Ref. 12) gave bisacodyl and sodium phosphates oral solution in combination. The time between sequential dosages differed from the petition and electrolyte data were not provided in the abstracts by Bawani et al. (Ref. 6) and Henderson et al. (Ref. 13).

The material from a postgraduate course given in May 1994 (Ref. 17) contains no new clinical data. However, the author concluded that sodium phosphates oral solution should not be used in patients with renal insufficiency, congestive heart failure, or cirrhosis with ascites because it may have deleterious effects. The chapter from a textbook titled "Colon and Rectal Surgery" (Ref. 9) did not contain any new clinical data that could be evaluated to support your petition.

We conclude that the data provided support the effectiveness of two 45-mL doses of sodium phosphates oral solution given 10 to 12 hours apart for bowel cleansing. However, we are concerned that this dosage regimen may not be safe for OTC use because of the electrolyte and vascular volume changes that occur. It is possible that this dosage regimen could be included under professional labeling only (i.e., labeling that is provided to health professionals, but not to the general public); however, adequate safety data, as described above, must be submitted. Therefore, we have determined that the data submitted in the citizen petition are insufficient to support the safety of two 45-mL doses of sodium phosphates oral solution in sequential administration 10 to 12 hours apart as a bowel cleansing system. This bowel cleansing system will not be included in the final monograph for OTC laxative drug products.

We intend to recommend to the Commissioner that the agency respond to your comments in the above manner in the final monograph for OTC laxative drug products, which will be published in a future issue of the FEDERAL REGISTER. Following publication, you may file a citizen petition to amend the final monograph or file a new drug application. Should the company

Peter S. Reichertz

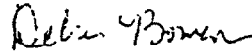
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wish to perform the clinical studies needed for this bowel cleansing system, we would be glad to review any proposed protocols. They may be submitted prior to publication of the final monograph.

Any comment you may wish to make on the above information should be submitted in three copies, identified with the docket number shown at the beginning of this letter, to the Dockets Management Branch (HFD-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857. This letter should not be considered a formal ruling on your petition. That occurs when you are sent a response by the Associate Commissioner for Regulatory Affairs.

We hope this information will be helpful.

Sincerely yours,



Debra Bowen, M.D.

Director

Division of OTC Drug Evaluation

Office of Drug Evaluation V

Center for Drug Evaluation and Research

Enclosure (References)

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ATTACHMENT B